UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,808	09/16/2003	Sylvie Roux	03495.0174-02000	2497

22852 7590 06/01/2006

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,808	ROUX ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-67* is/are pending in the application.

4a) Of the above claim(s) *36,38,39,42 and 44-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35,37,40,41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-24-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group VIII, including claims 32-35, 37, 40, 41 and 43, in the reply filed on 5-11-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 36, 38, 39, 42 and 44-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5-11-06.

Applicants' preliminary amendment filed 5-3-04 has been entered. Claims 1-31 have been canceled. Claims 37, 49 and 63 have been amended. Claims 66 and 67 have been added. Examiner thanks applicants for pointing out the filing of preliminary amendment on 5-3-04.

Claims 32-67 are pending. Claims 32-35, 37, 40, 41 and 43 are under consideration.

Specification

This application contains sequence disclosures that are encompassed by the definition for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no sequence identifier for the nucleotide sequence in Figures 1A and 1B or in the "BRIEF DESCRIPTION OF THE DRAWINGS". Each nucleotide sequence is required to have a sequence identifier. Appropriate correction is required.

Double Patenting

3. Claims 40 and 41 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 34 and 35. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 40, 41 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 depends from claim 39, which is a non-elected claim and is directed to using a TrkB receptor antagonist (not agonist), such as an antibody, that binds to a TrkB receptor agonist. It is unclear what is intended to claim in claim 40. Claims 41 and 43 depend from claim 40 but fail to clarify the indefiniteness.

6. Claims 32-35, 37, 40, 41 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to modulate the neuronal transport of the tetanus toxin or the fusion protein and whether the neuronal transport is modulated. The

method step only refers the administration of the TrkB agonist but fails to refer back to the preamble of the claimed method, i.e. modulating the transport in a neuron.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 32-34, 40 and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on using any TrkB receptor agonist or any neurotrophic factor that activates a TrkB receptor for modulating the neuronal transport of the tetanus toxin or the fusion protein in vitro or in vivo. The claims encompass a genus of TrkB receptor agonist or a genus of neurotrophic factor that activates a TrkB receptor. The specification only discloses that BDNF and NT-4 can activate TrkB receptor (see specification, [014], [0118]). The specification fails to disclose any other TrkB receptor agonist or any other neurotrophic factor that can activate TrkB receptor and fails to disclose the structural feature a TrkB receptor agonist that would activate TrkB receptor. The structural features of a TrkB receptor agonist that can distinguish said TrkB receptor agonist from the protein class has not been disclosed. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general,

guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify the claimed genus of TrkB receptor agonist or genus of neurotrophic factor that activates a TrkB receptor, and because they are highly variant, the BDNF and NT-4 as disclosed in the present application is insufficient to describe the claimed genus of TrkB receptor agonist or genus of neurotrophic factor that activates a TrkB receptor.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of claimed genus of TrkB receptor agonist or genus of neurotrophic factor that activates a TrkB receptor. Thus, it is concluded that the written description requirement is not satisfied for the use of TrkB receptor agonist or neurotrophic factor as claimed.

9. Claims 32-34, 40 and 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing the concentration of tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin in neuromuscular junction (NMJ) by injecting brain derivated neurotrophic factor (BDNF) or neurotrophin (NT) 4 into Levator auris longus (LAL) muscle or gastrocnemius muscle of mice, does not reasonably provide enablement for a method of modulating the neuronal transport of the tetanus toxin or the fusion protein comprising a fragment C of the tetanus toxin by using any TrkB receptor agonist or neurotrophic factor other than BDNF and NT-4 in vitro or in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 32-34, 40 and 43 are directed to a method of modulating the transport in a neuron of a tetanus toxin or a fusion protein comprising a fragment C of the tetanus toxin comprising administering to the neuron a TrkB receptor agonist, such as a neurotrophic factor, to modulate the neuronal transport of said tetanus toxin or fusion protein. Claim 33 specifies the TrkB receptor agonist increases the internalization of the tetanus toxin or fusion protein at a neuromuscular junction. Claim 43 specifies the neurotrophic factor is administered concurrently with the fusion protein.

The specification discloses that co-injection of GFP-TTC with either BDNF or NT-4 into Levator auris longus (LAL) muscle or gastrocnemius muscle of mice increases concentration of GFP-TTC at the neuromuscular junction as compared to control (e.g. p. 32-35, example 8-10). The claims encompass using any TrkB receptor agonist or any neurotrophic factor that activates a TrkB receptor for modulating the neuronal transport of the tetanus toxin or the fusion protein in vitro or in vivo. The specification only discloses that BDNF and NT-4 can activate TrkB receptor (see specification, [014], [0118]). As discussed above under 35 U.S.C. 112 first written description rejection, the specification fails to disclose any other TrkB receptor agonist or any other neurotrophic factor that can activate TrkB receptor and fails to disclose the structural feature a TrkB receptor agonist that would activate TrkB receptor. It appears that applicants, at the time the application was filed, do not have possession of any TrkB receptor agonist or neurotrophic factor that can activate TrkB receptor other than BDNF and NT-4. Thus, the claimed invention is not enabled other than the use of BDNF and NT-4.

Further, it was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed

from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7, IDS), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926, IDS) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins. Therefore, a proline-rich region within different context of amino acid sequences could contribute to different biological functions.

In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its

function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences. In view of the unpredictable biological function of a protein from mere amino acid sequence and the lack of information regarding the TrkB receptor agonist other than BDNF and NT-4, one skilled in the art at the time of the invention would not know how to use the full scope of the claimed TrkB receptor agonist to modulate the neuronal transport of the tetanus toxin or fusion protein in vitro or in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER